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The cardiac output optimisation following liver transplant (COLT) trial: a feasibility randomised controlled trial

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TITLE:

The Cardiac output Optimisation following Liver Transplant (COLT) trial: A feasibility randomised controlled trial.

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ABSTRACT

Background: Perioperative goal directed fluid therapy (GDFT) has been shown to reduce postoperative complications following major surgery; this intervention has not been formally evaluated in the setting of liver transplantation.

Methods: We conducted a prospective trial of GDFT following liver transplantation randomising patients with liver cirrhosis to either 12 hours of GDFT using non-invasive cardiac output monitoring or standard care (SC). The primary outcome was feasibility. Secondary outcomes included survival, postoperative complications (Clavien-Dindo), quality of life (by EQ-5D-5L) and resource use. Trial specific follow up occurred at 90 and 180 days after surgery.

Results: The study was feasible. Of 224 eligible patients,122 were approached,114 consented to participate and 60 were enrolled into the trial. The mean (SD) volume of IV crystalloid administered to the GDFT group during the 12-hour study period was 3968 (2073) ml for the GDFT group and 2510 (1026) ml for the SC group. As regards secondary outcomes there was no difference in survival or overall complication rates. There was no significant difference in quality of life scores and resource use between the groups.

Conclusion: A randomised study of GDFT following liver transplantation is feasible. A post-trial stakeholder meeting supported proceeding with a full multi-centre trial.

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INTRODUCTION

The volume and type of intravenous (IV) fluid that is given around the time of surgery as well as the manner in which it is administered directly affects patient outcomes.[1] Under-resuscitation can result in organ hypoperfusion and failure[2] whilst excessive IV fluid is equally harmful.[3, 4] One method of optimising fluid administration is goal-directed fluid therapy (GDFT), defined as the administration of IV fluid boluses to restore intravascular normovolaemia against a specific haemodynamic target.[5] Perioperative GDFT can be undertaken during and/or after surgery. Patients undergoing major surgery have been shown to benefit from perioperative stroke volume optimisation by GDFT, primarily in terms of reduced postoperative complications and length of hospital stay.[6–8] These advantages lead to improvements in postoperative quality of life, increased life expectancy and reduced costs to healthcare providers.[9–11] Estimation of a patient's intravascular volume status based on simple measures such as heart rate, blood pressure, central venous pressure and urine output is known to be inaccurate but remains standard of care during and after the majority of surgical procedures[12, 13] including liver transplantation. In patients with liver cirrhosis presenting for transplantation cirrhotic cardiomyopathy is common and can have a profound impact on cardiovascular function perioperatively.[14] The findings from GDFT studies in patients undergoing general abdominal surgery may therefore not be applicable to those requiring liver transplantation.

We undertook a feasibility randomised controlled trial (RCT) to assess the ability to enrol patients into a study of postoperative GDFT, successfully deliver the intervention and evaluate its safety profile in patients with liver cirrhosis undergoing transplantation.

METHODS

Study design

The protocol for this study has been published previously.[15] We conducted an RCT of GDFT versus standard IV fluid management in a single centre in the United Kingdom to assess the feasibility of conducting a postoperative fluid optimisation trial in patients who have undergone liver transplantation. Secondarily, we compared the intervention and standard care (SC) groups to assess the safety profile of GDFT and to collect information on clinical outcomes

and quality of life, evaluated potential primary outcomes for a subsequent trial to assess the efficacy of GDFT in liver transplantation and examined the cost effectiveness of the intervention.

Study setting

The study was reviewed and approved by University College London Bloomsbury Research Ethics Committee. Potential participants were identified from the liver transplantation waiting list or preoperative assessment clinic. Inclusion and exclusion criteria are shown in Table 1. All patients provided written consent. Following liver transplantation, at the time of admission to the intensive care unit (ICU), patients were randomised in a 1:1 manner into either the GDFT or SC group. The Sealed Envelope randomisation service was used to allocate patients. Randomisation was stratified according to whether the organ donor was deceased after cardiac death (DCD) or deceased after brain death (DBD). The donor retrieval and surgical implantation procedures used are outlined in the supplementary material.

Study intervention

GDFT or SC was commenced postoperatively on arrival to the ICU and continued for a total of 12 hours. In both groups, the participants were connected to an EV1000 Clinical Platform via a FloTrac transducer (Edwards Life Sciences, Irvine, USA) to provide continuous haemodynamic monitoring. All EV1000 data were recorded by a designated research nurse. In the GDFT group a protocol was used to optimise intravascular fluid volume (Figure 1). This protocol, administered by the trial research nurse, was initiated by giving a 250 ml bolus of IV Hartmann's solution over 5-10 minutes. If the SV increased by 10% or more after the bolus the participant was deemed to be fluid responsive, and a further monitored bolus was administered. The administration of fluid boluses was repeated until a rise of 10% or greater was no longer observed. Monitoring then continued until the SV fell by 10% or greater from this baseline; the bolus procedure was then repeated. No continuous maintenance IV fluid was given to patients in the GDFT group. All intervention fluid boluses were given by the

research nurse and the volume recorded on the bedside chart so that it could be seen by the clinical team. For participants in the SC group the research nurse documented haemodynamic variables from the EV1000 hourly but this information was blinded to the clinical team and the research nurse did not administer any IV fluid to participants. In the SC group, fluids were administered by the clinical team without information from the haemodynamic monitoring. In both groups, clinicians could administer additional IV fluids if they deemed it to be necessary; these choices were documented for the period of the intervention. All other medical management was similar between the two treatment groups, including the administration of blood products, which was not protocolised. At the end of the 12 hour study period, the EV1000 monitor was disconnected and the clinical team instructed to continue IV fluid management as they deemed clinically appropriate.

Outcome measures

The primary outcome of the study was feasibility, assessed using the following metrics: participant recruitment rate, protocol completion and deviations, and participant withdrawal. A predetermined recruitment of greater than 40% of patients fulfilling the criteria for this study was deemed to indicate success. A number of predetermined secondary outcomes were also measured (Table 2)[15], including postoperative complications[16]. Quality of life (QoL) was assessed by asking participants to complete an EQ-5D-5L assessment immediately prior to surgery, at discharge from hospital, and 90 and 180 days after surgery. Resource use data were collected during hospital admission and at the two follow-up points.

Statistical analysis

Data were collected onto a paper collection form and then transferred onto an electronic clinical record form (eCRF) – REDCap (Research electronic data capture[17]). Statistical analyses were carried out with STATA version 14 with the statistician blinded to the treatment arm. The two treatment groups were compared to ensure they had similar clinical characteristics using mean and standard deviation or median and inter-quartile range for

continuous variables, as appropriate, and counts and percentages for categorical variables. For feasibility outcomes, the proportion of patients who consented to be randomised was presented with a 95% confidence interval. The proportion of patients withdrawn from GDFT was also presented as well as the proportion of patients who deviated from the GDFT protocol for the 12 hour intervention period. For clinical outcomes, the difference in the proportion of people with a complication between the two groups was calculated with a 95% confidence interval. The median number and grade of complications were also presented. The median length of stay in ICU and hospital was presented for each group while the proportion of patients readmitted in ICU during the whole period of follow-up was also calculated. The mean difference in quality of life score between the two groups at each time point was presented with a 95% confidence interval. All other secondary outcomes were summarised for each group using mean profile plots over time and mean/median differences at baseline, 6 and 12 hours were presented as appropriate with 95% confidence intervals.

Economic analysis

For the economic analysis data on healthcare resources, patient survival and QoL were utilised. The EQ-5D-5L data were converted to an EQ-5D index score using a crosswalk algorithm.[18] Quality adjusted life years (QALYs) was further estimated by multiplying index scores by corresponding duration. Costs per patient was estimated based on resource use during the primary (transplant surgery) admission and subsequent healthcare usage. Multiplying the unit costs by each unit of resource use and summing these resource costs across each patient's six-month follow-up from date of operation enabled aggregation of total cost per patient. A value of 0 was assigned to resource use and utility after death if a patient died during trial period. Where possible, national estimates of unit prices was sourced from the NHS Reference Costs published by Department of Health (DH, 2017) and Personal Social Services Research Unit (PSSRU, 2017) to apply to resource use data from the COLT trial. The ICU cost was weighted by activity to calculate adult critical care costs for patients with liver disease. The cost of IV fluid replacement immediately following liver transplantation using

GDFT were identified from the hospital personnel including the cost of the EV1000 monitor and FloTrac transducers.

RESULTS

Patient enrolment

The study recruited patients from March 2016 - July 2017. The initial planned study size was 50 participants which was increased to 60 as the baseline QoL assessment was incomplete in the early stages of the study. A total of 224 eligible patients were sent a patient information sheet and of these 122 were formally approached either in an outpatient clinic or on the day of surgery (Figure 2). Of the 122 patients approached 114 consented to participate (93.4%, 95% confidence interval (CI) 87.5 to 97.1%) and 8 declined. None withdrew their consent. Of the 114 consented patients on the waiting list, 60 proceeded to transplant during the trial recruitment period and enrolled into the study. The reason that 54 consented patients were not randomised were: not undergoing transplant within the trial period (n=25), removed from the waiting list for clinical reasons (n=14), research team not available (n=9), enrolled into another RCT (n=5) and died on the transplantation waiting list (n=1). The median recruitment rate was 4 participants per month. The median (IQR) age of participants was 53.2 (10.9) years, and 43/60 (71.7%) were female. The recipient baseline and donor characteristics according to treatment group are shown in Table 3.

Intervention period

All patients completed the 12 hour trial treatment. There were seven protocol deviations in the GDFT group and one in the SC group; all were deemed to be minor deviations. No participants were withdrawn from the trial treatment at the request of the clinical team

There was no difference in heart rate, systolic blood pressure, SV, cardiac output or cardiac index between the two groups at baseline, hour 6 or hour 12 post-transplant. Diastolic blood pressure was higher in the GDFT group at baseline (62.7 (10.19)) versus 55.3 (9.11) mmHg

(mean difference: 7.4 (95%CI: 2.41 to 12.39)), but not at 6 or 12 hours. The mean difference in cardiac output change from baseline to hour 6 between the two groups was -1.53 l (95% CI: -2.95 to -0.11), mixed venous oxygen saturation was higher in the SC group at 12 hours (77.57 % (4.86) versus 69.9 (6.97), mean difference: -7.67 (95%CI: -14.2 to -1.15)) although there were only 7 and 10 patients with these data in respective groups. Mean haemodynamic measures during the 12 hour treatment period are shown for each group in the supplementary material.

Trial treatment

The mean (SD) volume of IV crystalloid fluid administered to the GDFT group during the treatment period was 3968 (2073) ml for the GDFT group and 2510 (1026) ml for the SC group. Additional fluid and blood products administered to participants is detailed in Table 4; the mean (SD) total fluid volume administration (including blood products) during the treatment period was 5316 (2334) ml for the GDFT group and 3807 (1345) ml for the SC group.

Completeness of follow up data collection

Clinical follow up data was complete for 60/60 (100%) at hospital discharge, 58/58 (100%) at 90 days and 56/57 (98.3%) at 180 days. For QoL data this was 55/58 (94.8%), 56/57 (98.2%) and 56/57 (98.2%) respectively.

Secondary outcomes

There were no differences in the mortality rate and overall number and severity of complications between the 2 groups (Table 5). Grade III complications (those requiring intervention) were increased in the GDFT group (19 (63.3%) versus 6 (20%), difference in proportion: 43.3 (95%CI: 20.9 to 65.7)). The detailed breakdown of complications is shown in the supplementary online data. Most complications occurred during the postoperative hospital stay.

Dividing the complications into organ-specific domains according to the postoperative morbidity survey (POMS) classification[19] there were no differences between the two groups during their hospital admission. At 90 days there were more neurological complications in the GDFT group than the SC group (11 (40.7%) versus 1 (3.6%), difference in proportion: 37.2 (95% CI: 17.4 to 56.9)). At 180 days there were more cardiovascular complications in the SC than the GDFT group (8 (30.8%) versus 1 (3.6%), difference in proportion: -27.2% (-46.2 to -8.2). Liver transplantation-specific complications in each group are shown in the supplementary material. The total number of patients with at least one liver transplantation-specific complication was not different between the groups at discharge from hospital, 90 day or 180 days. There were 6 (20%) occurrences of biliary leak requiring intervention in the GDFT group compared to 1 (3.3%) in the SC group (difference in proportion: 16.7 (95%CI: 1 to 32.4)).

The median ICU length of stay was 3.5 (3-10) days in the GDFT group and 3.0 (2-8) days in the SC group (p=0.673); median hospital length of stay was 26.0 (18-41) days for the GDFT group and 23.0 (15-30) days for the SC group (p=0.473). Five patients had at least one readmission to ICU from GDFT (16.7%) group and three (10%) from the SC group, but this not statistically significant (difference in proportion: 6.7% (95%: -10.5 to 23.8).

Economic Analysis

A total of 13 patients, 5 from GDFT group and 8 from SC group had one or more missing EQ-5D assessment or resource use at different time points. Complete case analysis was adopted to estimate incremental QALY and incremental cost for each patient. This approach reduced the sample size to 25 patients in GDFT group and 22 patients in SC group. A summary of utility estimates for the two arms over the trial period is provided in Table 6. The QoL score in the GDFT group was lower than the SC group at each time period. However, the difference in score between the two groups was not statistically significant at any time point.

The QALY for the GDFT and SC groups over the trial period is summarised in Table 7. In the six-month follow up, the average QALYs in the GDFT group were slightly lower than in the SC group. The difference was -0.014 and was not statistically significant (p=0.68).

The mean inpatient stay in GDFT group was lower than the SC group in term of length of stay (Table 8). The difference in resource use was not statistically significant at any time point. The average cost of inpatient stay during primary admission and six-month follow up for GDFT group was £59,233, which was lower than the SC group at £60,743. However, the difference of £1,509 was not statistically significant.

DISCUSSION

We set out to determine whether it was feasible to carry out a study of postoperative GDFT in patients with liver cirrhosis who had undergone liver transplantation. We successfully recruited 93.4% of approached patients, without any being withdrawn from the study and with few protocol deviations. Compliance with follow-up data collection was 95% or more of the participants at 180 days. This demonstrates that under trial conditions, GDFT can be delivered on an ICU following liver transplant surgery. The principle finding was that patients were extremely motivated to participate in research of this nature. We enrolled a median of 4 participants per month, which compares favourably to the median of less than 1 per month found in a recent review of UK NIHR funded trials.[20] GDFT was considered acceptable to clinicians as no patients had their study treatment terminated.

During the 12 hour treatment period the median volume of crystalloid received by the GDFT group was greater than received by the SC group. A previous retrospective 'before and after' study of GDFT in liver transplant showed reduced fluid administration and improved clinical outcomes with 48hrs of GDFT.[21] Differences may be due to the non-randomised nature of the previous study or the increased duration of GDFT. Whether optimal fluid balance perioperatively improves clinical outcomes remains debatable.[4, 22] Some of this debate is due

to lack of clarity of definitions along with poor study design.[23] A 'zero-balance' approach has been advocated for patients in enhanced recovery after surgery programmes[24] and weight gain postoperatively (due to fluid accumulation) can lead to an increase in complications and hospital length of stay.[25] A cumulative positive postoperative fluid balance following liver transplant has also been independently associated with the development of acute kidney injury and a requirement for renal replacement therapy.[26] Whilst there were few statistical differences between the GDFT and SC groups in haemodynamic measures collected during the study intervention period, there were a number of interesting trends that suggest a positive effect of the intervention during that time (see supplementary online material).

This study was not powered to detect differences in secondary outcomes between study groups. However, they were calculated in order to assess their value as endpoints for future studies and to identify any possible harms associated with the intervention. In terms of postoperative complications, there were no overall differences in number and severity of complications between the groups. Increased incidences within small sub-groups, such as those with grade 3 complications or with bile leaks, are likely to be related to the small patient numbers involved. This would, however, have to be reviewed within the context of a larger trial.

The optimal period and duration of GDFT remains unclear. We anticipated that intraoperative GDFT would not be possible due to the rapidly changing haemodynamic landscape during transplant surgery. This is not to say that it will never be possible and the previously mentioned study has to some extent explored its feasibility during transplant surgery.[21] The type of device used to measure haemodynamic variables varies widely between studies and it is not clear whether benefits demonstrated with one technology can be translated to other technologies.[27, 28] We elected to use an uncalibrated pulse contour analysis device, the EV1000 FloTrac system (Edwards Life Sciences, Irvine, USA) as all patients undergoing liver transplant would have an arterial catheter inserted as part of routine clinical practice. A similar device, the

FloTrac-Vigileo (Edwards Lifesciences, Irvine, USA) has been compared alongside a calibrated pulse contour analysis monitor (LiDCO Plus - LiDCO Ltd., London, UK) and neither performed well compared to pulmonary artery catheter thermodilution measurements of cardiac index during orthotopic liver transplant.[29] It has previously been reported that the FloTrac-Vigileo had clinically acceptable bias and precision when compared to pulmonary artery catheter thermodilution in patients undergoing liver transplant, although it underestimated pulmonary artery catheter measurements at higher cardiac outputs.[30]

QoL assessed by the EQ-5D-5L indicated a slightly lower utility estimate for patients at all time periods and lower QALY value with GDFT than the SC group. However, these differences were not significant. In terms of overall hospital resource use, the total costs were lower for the GDFT group because of a shorter inpatient stay compared to SC group. Due to some missing QoL observations a complete case analysis was conducted. However, this approach could allow a selection bias for complete data in those with a better QoL score. For example, a patient who died during follow up was excluded from the complete case analysis because the resource use data before death was unavailable. The economic analysis was preliminary and should be investigated in a larger sample size in the future.

One of the major strengths to this study is that in the GDFT group the fluid was administered by the trial research nurse according to the pre-defined protocol and in the SC group the cardiac output data were collected but the data was hidden from the clinical team. This minimised the risk of bias in fluid management. However, the clinical team would be aware which arm of the study the patient had entered and hence it was felt necessary to declare all fluid boluses and record them on the patient's clinical chart. Thus, unidentified confounding factors could have influenced the results of the study. Importantly, those analysing the data were blinded to the allocated group of the participants in the database. Another limitation is that the study was only conducted in a single centre, a design which is known to lead to a larger intervention effect than multicentre studies.[31] Relevant to our feasibility outcome is the

fact that single-centre studies in the UK tend to have a higher recruitment rate than the individual sites of multicentre studies.[20] There were more protocol deviations in the GDFT group compared to the SC group, which was not a surprising finding as the protocol for the intervention in the GDFT group was complicated compared to SC group. All of the deviations were determined to be minor, so are unlikely to have exerted a significant impact on the results.

In conclusion we have demonstrated the feasibility of conducting a study of postoperative GDFT in patients with cirrhosis following orthotopic liver transplantation. Although some complications were more common with GDFT the overall complication rate was no different to SC. In this feasibility study we were unable to ascertain whether or not GDFT was of clinical benefit as this was not the purpose of the trial. A stakeholder meeting with patient representatives supported proceeding to a larger multicentre study to demonstrate efficacy and cost effectiveness.

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TABLES

Table 1. Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Adult patients (aged between 18 and 80 years)	Non-cirrhotic liver disease
Diagnosis of liver cirrhosis	Pregnancy
Selected to undergo liver transplantation at the Royal Free Hospital	Age less than 18 years or over 80 years
Competent to give consent	Body weight less than 40 kg
	Re-transplantation for primary graft non-function
	Fulminant hepatic failure
	Emergency surgery
	Known learning disabilities or previously lacking capacity to consent for themselves
	Prisoners
	Patients already enrolled in an interventional study
	Refusal or inability to consent

Table 2. Secondary outcome measures

Secondary outcome measures
Quality of life scores: at hospital discharge, 90 and 180 days post-surgery
Length of ICU stay (days)
Length of hospital stay (days)
Survival: at hospital discharge, 90 and 180 days
Postoperative complications: at hospital discharge, 90 and 180 days *
Specific liver transplantation-related complications: at hospital discharge, 90 and 180 days

* defined by Clavien-Dindo classification[16] and the Postoperative Morbidity Survey (POMS) organ systems[19]

Table 3. Recipient baseline and donor characteristics

	GDFT group (n=30)	SC group (n=30)
Recipient baseline details		
Mean (SD) Age	51.16 (10.4)	54.7 (11.2)
Male (%)	20 (66.7%)	23 (76.7%)
Recipient MELD	15.4 (5.6)	15.0 (5.4)
Recipient UKELD	54.5 (4.7)	54.0 (4.9)
EQ-5D-5L* (n=54)	0.8 (0.2)	0.8 (0.1)
Reason for transplantation		
Alcohol-related cirrhosis	11 (36.7%)	12 (40.0%)
Hepatitis C	3 (10.0%)	9 (30.0%)
Hepatitis B	4 (13.3%)	2 (6.7%)
Autoimmune hepatitis	2 (6.7%)	1 (3.3%)
Primary biliary cirrhosis	6 (20%)	4 (13.3%)
Primary sclerosing cholangitis	2 (6.7%)	0 (0%)
other	9 (30%)	10 (33.3%)
Donor details		
Donor Age (years) †	49.8 (17.3)	44.9 (18.9)
Donor BMI†	25.6 (4.2)	24.6 (3.8)
Cold Ischaemic time (hours)†	7.2 (2.6)	7.3(2.7)
DBD [heart beating] (%)	24 (80.0%)	25 (83.3%)
DCD [non-heart beating] (%)	6 (20.0%)	5 (16.7%)

Donor Liver Appearance*		
Healthy	19 (70.4%)	23 (76.7%)
Suboptimal	8 (29.6%)	7 (23.3%)
Donor Liver Steatosis*		
None	13 (44.4%)	21 (70.0%)
Mild	9 (33.3%)	7 (23.3%)
Moderate	6 (22.2%)	2 (6.7%)
Donor Liver Capsular Damage*	2 (7.1%)	4 (13.3%)
Graft Type		
Split liver	4 (13.3%)	3 (10.0%)
Whole liver	26 (86.7%)	27 (90.0%)
OLT Type		
Conventional	10 (33.3%)	14 (46.6%)
Piggy back	20 (66.7%)	16 (53.3%)

Data is presented in Means and SD

† 1 missing value in GDFT group for donor age, BMI and CIT

* 3 missing values in GDFT group for donor liver appearance, steatosis and capsular damage

Table 4. Mean (SD) intravenous fluid and blood products administered during the study intervention period

	GDFT group	**SC group**
Crystalloid (ml)	3968 (2073)	2510 (1027)
Additional fluid volume (ml)*	864 (609)	779 (473)
Total fluid input (ml)	5317 (2335)	3807 (1345)
Blood products		
20% Human Albumin Solution (ml)	93 (295)	74 (209)
Packed red blood cell (ml)	177 (456)	150 (316)
Fresh frozen plasma (ml)	81 (233.7)	145 (323)
Cryoprecipitate (ml)	71 (394.0)	73 (157)
Platelets (ml)	62 (175)	76 (165)

* primarily fluid used to dilute intravenous medications

Table 5. Number (%) of patients in each group with at least one complication by Clavien-Dindo grade during their hospital admission.

		GDFT group		SC group			
Time-point	**Clavien-Dindo grade**	**N**	**Freq (%)**	**N**	**Freq (%)**	**Difference in proportion (95%CI)**	**p-value**
Discharge	I	30	27 (90)	30	26 (86.7)	3.33% (-12.89 to 19.56)	0.688
	II	30	17 (56.7)	30	22 (73.3)	-16.67% (-40.43 to 7.1)	0.176
	III	30	19 (63.3)	30	6 (20.0)	43.33% (20.92 to 65.74)	0.001
	IV	30	16 (53.3)	30	14 (46.7)	6.67% (-18.58 to 31.91)	0.606
	V	30	1 (3.3)	30	1 (3.3)	0% (-9.08 to 9.08)	0.754
90 days	I	27	24 (88.9)	28	19 (67.9)	21.03% (0.06 to 42)	0.059
	II	27	16 (59.3)	28	17 (60.7)	-1.46% (-27.35 to 24.44)	0.912
	III	27	7 (25.9)	28	8 (28.6)	-2.65% (-26.17 to 20.88)	0.826
	IV	27	1 (3.7)	28	0 (0)	3.7% (-3.42 to 10.83)	0.304
	V	27	0 (0)	28	1 (3.6)	-3.57% (-10.45 to 3.3)	0.509
180 days	I	28	15 (53.6)	26	15 (57.7)	-4.12% (-30.61 to 22.37)	0.761
	II	28	12 (42.9)	26	7 (26.9)	15.93% (-9.1 to 40.97)	0.221
	III	28	9 (32.1)	26	8 (30.8)	1.37% (-23.4 to 26.15)	0.914
	IV	28	0 (0)	26	0 (0)	/	
	V	28	0 (0)	26	0 (0)	/	
Total period	I	30	30 (100)	30	28 (93.3)	6.67% (-2.26 to 15.59)	0.246
	II	30	27 (90)	30	27 (90)	0% (-15.18 to 15.18)	0.665
	III	30	23 (76.7)	30	19 (63.3)	13.33% (-9.61 to 36.28)	0.260
	IV	30	16 (53.3)	30	14 (46.7)	6.67% (-18.58 to 31.91)	0.606
	V	30	1 (3.3)	30	2 (6.7)	-3.33% (-14.33 to 7.66)	0.5

GDFT = Goal directed fluid therapy; SC = standard care

Table 6. Quality of life measured by EQ-5D index score

	GDFT group			SC group			
Variable	Obs.	Mean (a)	Std. Dev.	Obs.	Mean (b)	Std. Dev.	Difference (a-b)
Baseline	25	0.799	0.18	22	0.821	0.14	-0.022
Discharge	25	0.641	0.32	22	0.642	0.24	-0.001
90 day	25	0.698	0.29	22	0.746	0.26	-0.047
180 day	25	0.726	0.30	22	0.780	0.22	-0.055

GDFT = Goal directed fluid therapy; SC = standard care

Table 7. Mean QALY by treatment group arm

QALY	**Obs.**	**Mean**	**95% CI**
GDFT group	25	0.350	0.30 to 0.41
SC group	22	0.365	0.32 to 0.41
Difference		-0.014	-0.84 to 0.06

GDFT = Goal directed fluid therapy; SC = standard care

Table 8. Mean number and type of hospital bed days by arm.

	GDFT group			SC group			
Variable	Obs.	Mean (a)	Std. Dev.	Obs.	Mean (b)	Std. Dev.	Difference (a-b)
ICU	25	6.8	10.4	22	6.8	8.7	0
Ward	25	13.6	10.3	22	15.7	12.1	-2.1
ICU at 90 day	25	6.2	10.3	22	6.3	8.8	-0.1
Ward at 90 day	25	19.7	14.6	22	21.0	14.6	-1.3
ICU at 180 day	25	6.2	10.3	22	6.3	8.8	-0.1
Ward at 180 day	25	23.1	16.1	22	22.8	16.0	0.3

ICU = intensive care unit; GDFT = Goal directed fluid therapy; SC = standard care

FIGURES

Figure 1. Goal-directed fluid therapy protocol for the intervention group

Figure 2. CONSORT diagram for the COLT trial

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